RESEARCH PLAN PROPOSAL

"Michael Addition of some amines"

For registration to the degree of

Doctor of Philosophy

IN THE FACULTY OF SCIENCE

THE IIS UNIVERSITY, JAIPUR

Submitted by

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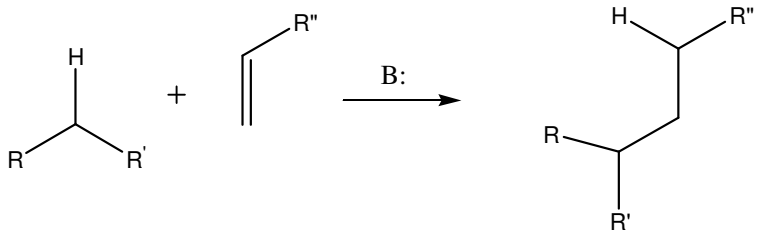
1. Introduction and Background information

The Michael reaction or Michael addition is the nucleophilic addition of a carbanion or another nucleophile[1,2,3] to an α,β-unsaturated carbonyl compound. It belongs to the larger class of conjugate additions. This is one of the most useful methods for the mild formation of C-C and other such bonds[4]. Many asymmetric variants exist[5,6].



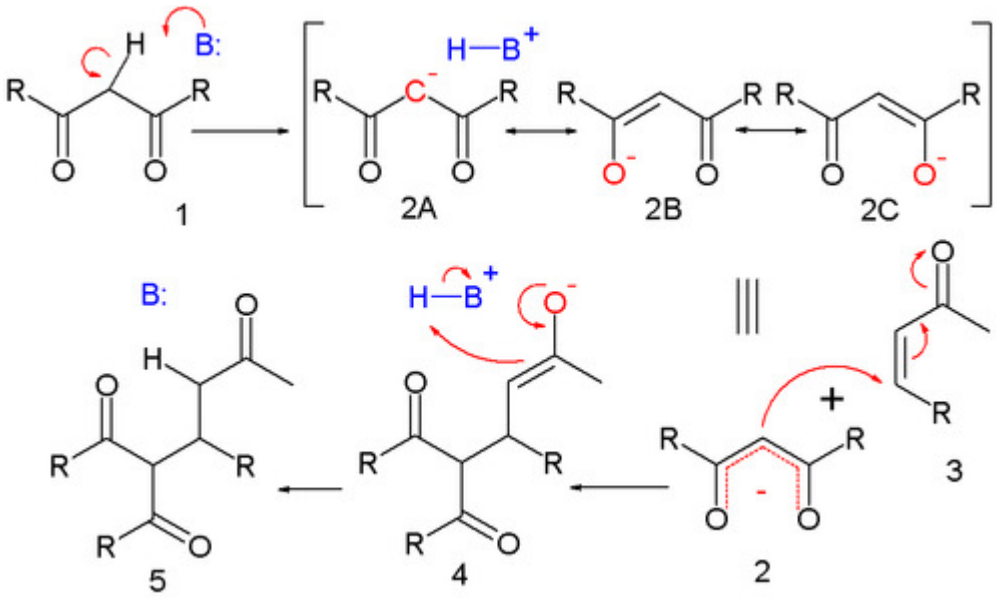
R" = CO, CN, NO_2 group etc.

Scheme 1: Michael addition reaction

In this scheme, the R and R' substituents on the nucleophile (a **Michael donor**) are electron-withdrawing groups such as acyl and cyano making the methylene hydrogen acidic forming the carbanion on reaction with a base **B:**. The substituent on the activated alkene, also called a **Michael acceptor**, is usually a ketone making it an enone, but it can also be a nitro or cyano group.

As originally defined by Arthur Michael,[7,8] the reaction is the addition of an enolate of a ketone or aldehyde to an α,β-unsaturated carbonyl compound at the β carbon. A newer definition, proposed by Kohler[9] is the 1,4-addition of a doubly stabilized carbon nucleophile to an α,β-unsaturated carbonyl compound. The Michael addition is an important atom-economical method for diastereoselective and enantioselective C-C bond formation. Subsequently the scope of the Michael addition has been further enlarged by including other nucleophiles, such as amine, amides, etc as Michael donors. **Thus Michael addition can be defined as 1,4-addition of a nucleophile to an activated alkene.**

The reaction mechanism is shown in scheme 2 (with R an alkoxy residue):



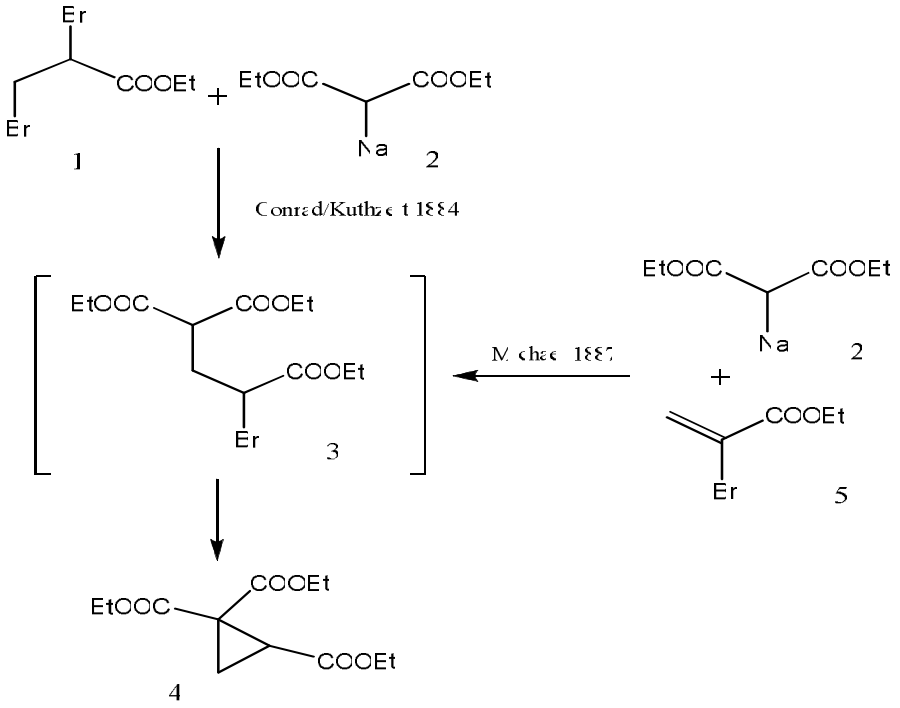
Scheme 2: Mechanism of Michael addition

Deprotonation of **1** by base leads to carbanion **2** stabilized by its electron-withdrawing groups. Structures 2A to 2C are three resonance structures that can be drawn for this species, two of which have enolate ions. This nucleophile reacts with the electrophilic alkene **3** to form **4** in a conjugate addition reaction. Proton abstraction from protonated base (or solvent) by the enolate **4** to **5** is the final step.

2. Review of Literature

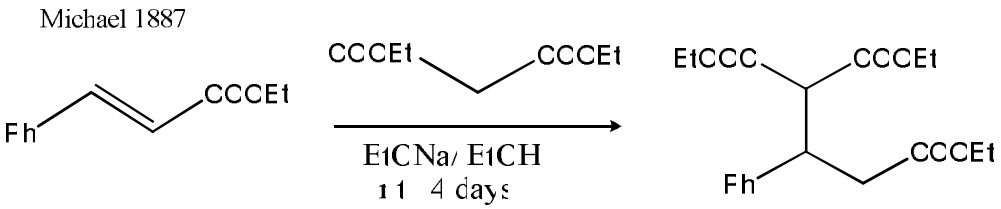
Over the years, the scope of Michael reaction has increased dramatically to include a broad range of acceptors and the Michael-type additions of non-carbon donors.

The research done by Arthur Michael in 1887 was prompted by an 1884 publication by Conrad & Kuthzeit on the reaction of ethyl *2,3-dibromopropionate* with *diethyl sodiomalonate* forming acyclopropane derivative[10] (now recognized as involving two successive substitution reactions).



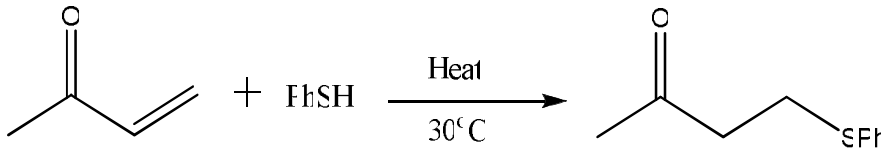
Scheme 3

Michael was able to obtain the same product by replacing the propionate by *2-bromacrylic acid ethylester* and realized that this reaction could only work by assuming an addition reaction to the double bond of the acrylic acid. He then confirmed this assumption by reacting diethyl malonate and the ethyl ester of cinnamic acid forming the very first Michael adduct[11].



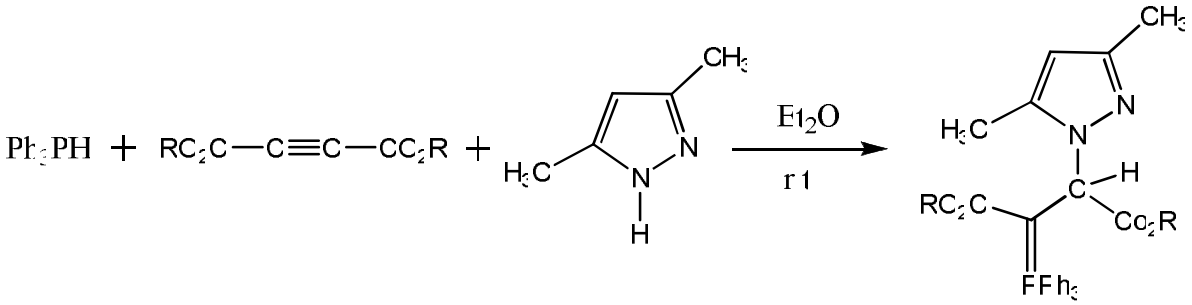
Scheme 4

A simple and efficient protocol has been introduced for the Michael addition of thiols to α,β-unsaturated carbonyl compounds under solvent-free conditions without the use of a catalyst[12].



Scheme 5

Stable crystalline phosphorus ylides were obtained in excellent yields from the 1:1:1 addition reactions between triphenylphosphine and dialkylacetylene dicarboxylates in the presence of an NH-acid, such as 3,5-dimethylpyrazole[13].



Scheme 6

A series of secondary amine-thiourea catalysts derived from L-proline and chiral diamine were prepared and successfully applied to the Michael addition of acetone to *trans*-nitroalkenes in excellent yields (up to 99%) and enantioselectivities (44-91% ee)[14].

Conjugate addition of 2-(bromomethyl)- and 2-(2-bromoethyl)piperidinehydrobromide to methyl and ethyl acrylate in the presence of triethylamine afforded the corresponding 3-[2-(bromomethyl)piperidin-1-yl]propanoates and 3-[2-(2-bromoethyl)piperidin-1-yl]propanoates for the first time. Furthermore, methyl 3-[2-(bromomethyl)piperidin-1-yl]propanoate was converted into the novel 2-(methoxycarbonyl)indolizidine upon treatment with lithium diisopropylamide in THF. The latter ester was easily reduced by means of lithium aluminium hydride in diethyl ether, affording 2-(hydroxymethyl)indolizidine in high yield[15].

Several primary and secondary amines were added to α,β-unsaturated esters, nitriles, amides and ketones to give the corresponding saturated amines mediated by solid lithium perchlorate under solvent free and environmentally friendly conditions at room temperature[16].

3. Objectives

- Michael addition reaction of secondary amines with Maleic anhydride and similar compounds.
- Michael addition reaction of primary amines with Maleic anhydride and similar compounds.
- Stereoselective Michael addition of amines to Maleic anhydride and similar compounds.
- To establish the structures and properties of the above compounds using NMR, IR and X-Ray Crystallography.
- To investigate theoretically the mechanism of the reaction and determine order of reactivity of various amines.

4. Significance

The aza-Michal addition is one of the widely used reactions for carbon-nitrogen bond formation[17]. Conjugate reaction of various amines with α,β-unsaturated carbonyl compounds provides β-amino carbonyls, which are useful synthons for the preparation of several nitrogen containing bioactive natural products[18], antibiotics[19], and chiral auxiliaries[20].

Michael addition is the first step for preparing dendrimers by divergent methods. So, we can also prepare some phosphorus-containing dendrimers through further reactions of these Michael addition products.

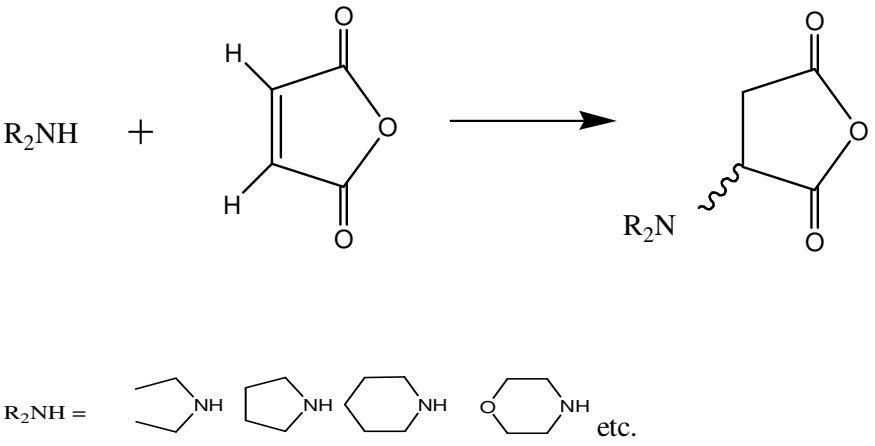
5. Hypothesis

The whole problem is based on Michael addition which is a 1,4-addition of the nucleophile to an activated alkene.

6. Plan of work and Methodology

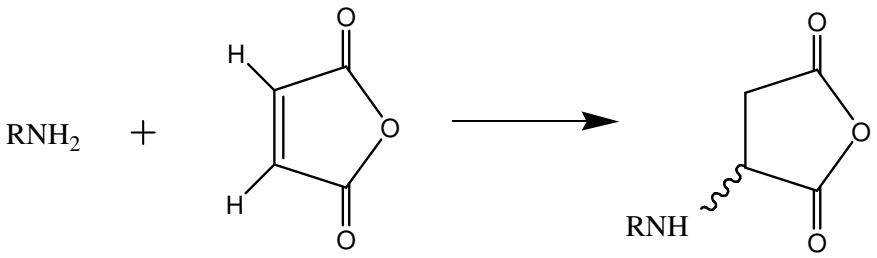
6.1 Proposed work

6.1.1 Michael addition of secondary amines with maleic anhydride and similar compounds[21,22]



Scheme 7

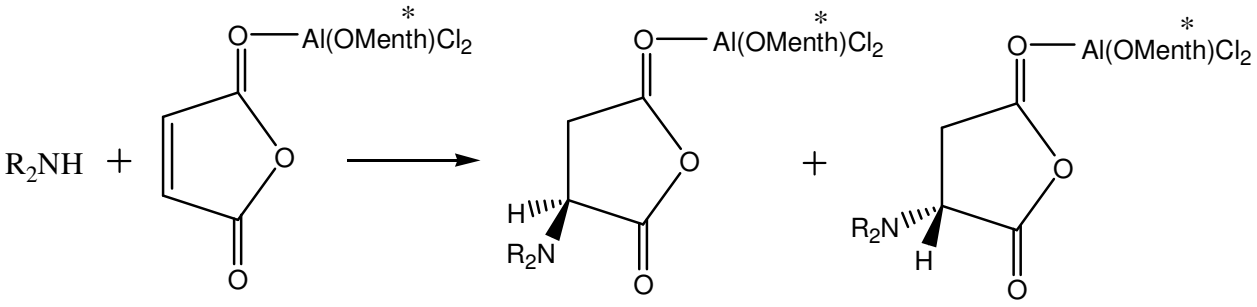
6.1.2 Michael addition reaction of primary amine with Maleic anhydride[21,22]



R1=C_6H_5-CH_2-, C_6H_5-, p-Cl-C_6H_5-, p-Cl-C_6H_5-CH_2-, p-CH_3-C_6H_5-, p-MeO-C_6H_5- etc.

Scheme 8

6.1.3 Stereoselective Michael addition of amines to maleic anhydride and similar compounds



Scheme 9

6.2 Methodology

Michael addition: The procedure described in the paper Janck Peterson; Arkadi Ebber; Veiko Allikmaa and Morgns Lopp, *Proc. Estonian Acad. Sci. chem.*, **2001**, *50*, 3,156-166 will be followed.

7. Year- wise plan of work and targets to be achieved

- **First year-** Michael addition reaction of secondary and primary amines with Maleic anhydride and similar compounds.
- **Second year –** Stereoselective Michael addition of amines to Maleic anhydride and similar compounds.
- **Third year –** Consolidation, compilation and the publication of above results.

8. Place of Work and Facilities available

Department of chemistry, IIS University, Jaipur. A modern laboratory modestly equipped with instruments is available.

9. Limitation and Alternative Plan of Study

The non-availability of multinuclear NMR spectrometer is the main limitation. We shall try to take the help of the other institutions where this instrument is available.

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